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REVIEW

Metastatic Breast Cancer: Focus on Capecitabine

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Abstract: Capecitabine is an oral 5-fluorouracil pro-drug with activity in metastatic breast cancer. As a single agent, response rates of 30%–30% and 15%–30% have been reported in first-line and more heavily pretreated populations, respectively. Capecitabine in combination with chemotherapy and biologic agents has resulted in significant improvement in the clinical endpoints of overall survival, response rates, and time to progression. Capecitabine has unique toxicities, which are manageable with proper dosing, vigilance, patient education and incorporation of dose interruptions and supportive care measures. This review will critically discuss the data on the efficacy of capecitabine in metastatic breast cancer.

Keywords: breast neoplasm, cancer, 5-fluorouracil, fluoropyrimidines

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Introduction

With an estimated 192,370 new cases and 40,170 deaths in the US in 2009, breast cancer remains one of the leading causes of cancer related mortality in women.[1] Over the past twenty years, breast cancer mortality has certainly declined with advances in treatment and earlier detection. However, metastatic breast cancer remains incurable, with only 15%–20% of patients surviving at five years (www.cancer.org). Hormone receptor status, HER2/neu amplification or overexpression, number of metastatic sites and tumor burden, patient age and co-morbidities, and interval between initial diagnosis and relapse are some of the important prognostic factors to consider in the treatment of advanced disease. Several choices are available for the treatment of metastatic breast cancer, ranging from cytotoxic chemotherapy, to targeted (biologic) therapy, to endocrine therapy. The decision is made based on the above tumor and patient characteristics and the available choices of therapy can potentially be sequenced over time.

Cytotoxic chemotherapy is an option for all patients with advanced breast cancer. Chemotherapy remains the only standard treatment for hormone receptor negative disease. In patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive advanced breast cancers, chemotherapy may be chosen initially due to visceral metastases or heavy tumor burden and associated severe symptomatology. Progression of disease in hormone-sensitive breast cancer may eventually result in endocrine resistance, at which point, palliative chemotherapy is the main therapeutic option. For Her2/neu-positive disease, chemotherapy in combination with Her2-directed therapy, such as trastuzumab or lapatinib, results in improved clinical outcomes compared to chemotherapy alone.[2,3] The same results have been seen with the strategy of aromatase inhibitors and HER2-directed therapy in ER- and/or PR-positive metastatic breast cancer.[4,5]

If the decision is made to treat with chemotherapy, metastatic breast cancer is fortunate to have many therapeutic options. The classes of active cytotoxic chemotherapy include anthracyclines, taxanes, anti-metabolites including capecitabine, vinca alkaloids, and epothilones, among others. Chemotherapy may be combined or administered as single agents. Additionally, biologics such as bevacizumab may be combined with chemotherapy to improve response rates and to prolong progression free survival.[6–8] The choice of which agent and how to administer it is often made based on prior therapies, side effect profile, ease of administration and convenience.

Capecitabine is an oral fluoropyrimidine carbamate, a 5-flurouracil (FU) pro-drug activated by thymidine phosphorylase. Capecitabine was first approved for use in metastatic breast cancer in 1998. It is currently FDA-approved in the treatment of adjuvant and metastatic colorectal cancer and in metastatic breast cancer in combination and as a single agent after progression with paclitaxel and anthracyclines. Due to the ease of oral administration and manageable toxicity profile, in clinical practice, capecitabine is often the first agent of choice as a single agent or in combination with cytotoxics or biologics.

In this review, we will discuss the pharmacology and mechanism of action and the toxicities of capecitabine. We will critically review the data supporting its use in metastatic breast cancer, as well as a phase III study of capecitabine in early stage breast cancer in the elderly. Finally, we will discuss management of the most common side effects and assess the role of capecitabine in breast cancer.

Pharmacology of Capecitabine

Flourouracil (5-FU, FU), an antimetabolite, was originally synthesized in 1957. Its mechanism of cytotoxicity is through inclusion of the drug into the replicating RNA and depletion of thymidine due to binding with the enzyme thymidylate synthase. However, intravenous administration of FU is required due to variable gastrointestinal absorption and rapid degradation. Capecitabine was developed with the goals of improved convenience through oral administration and improved safety and efficacy, by selective delivery of active drug to target tumor cells, sparing healthy tissue.[9] The chemical structures of capecitabine and fluorouracil are shown in Figure 1. The oral bioavailability of capecitabine is almost 100 per cent. It is metabolized to the only active compound, FU, via three metabolic steps. After intestinal absorption, liver carboxyl esterase converts capecitabine to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then metabolized to 5'-DFUR by cytidine deaminase, an

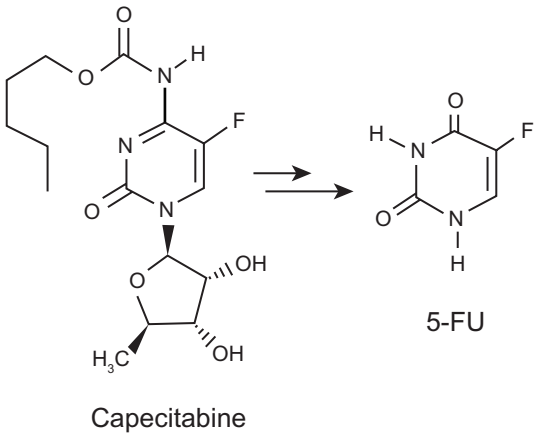

Figure 1. Chemical structures of capecitabine and fluorouracil.

ubiquitous enzyme with high concentrations in the liver, plasma and tumor tissue. 5'-DFUR is converted to FU by thymidine phosphorylase. This final enzyme required for the conversion of capecitabine to FU is found in amounts three to ten times higher in solid tumors compared with normal adjacent tissue. FU is degraded by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites which are eliminated renally. Hence DPD deficiency, present in two to four per cent of the population, leads to an increased risk of FU toxicity.

Due to renal clearance, capecitabine is contraindicated in patients with renal failure with a creatinine clearance less than 30 mL/minute.[10] In patients with a creatinine clearance of 30–50 mL/minute, 75% of the dose is recommended. Full dose is recommended with a creatinine clearance >50 mL/minute. Capecitabine dosing adjustments for hepatic dysfunction are currently not recommended, although limited data exist in this setting.

Capecitabine Toxicity

The early trials of single agent capecitabine utilized 2510 mg/m^2 daily in two divided doses on days 1–14 of a 21-day cycle.[11,12] The most common toxicities in the trial by Blum et al included hand-foot syndrome (56%), diarrhea (54%), nausea (52%), vomiting (37%), and fatigue (36%).[11] Stomatitis was reported in 9% of patients. The most common grade 3 and 4 toxicities were hand-foot syndrome (10%), diarrhea (14%), and fatigue (7%). Grade 3 and 4 hematologic toxicities were uncommon with 3% having neutropenia, 4% anemia and 4% thrombocytopenia. Interestingly, alopecia was not reported.[11] Similar rates of toxicties were noted in the first-line single agent trial.[12]

Not surprisingly, when capecitabine is combined with other agents, toxicities increase. For example, O'Shaughnessy et al combined docetaxel with capecitabine in patients with metastatic breast cancer and prior anthracycline exposure.[13] In this trial, the most common grade 3 and 4 toxicities with the combination were neutropenic fever (26%, most grade 4), hand-foot syndrome (24%), stomatitis (17%), neutropenia requiring medical intervention (16%, most grade 4), and diarrhea (15%). Two-thirds of patients in the combination arm required dose reduction.

Subsequent studies have utilized lower doses of capecitabine, both as single agent and in combination. These doses have reduced side effects, and sub-analyses have shown that lower doses have not impacted outcomes.[14]

Capecitabine Efficacy: Clinical Trials

Capecitabine has been studied as a single agent and in combination regimens in metastatic breast cancer, in both first-line treatment and in a more heavily-pretreated population. Here, we will review some of the pivotal studies.

Single agent activity

Table 1 summarizes the studies of single agent capecitabine in the first-line treatment of metastatic breast cancer. O'Shaughnessy et al compared capecitabine with intravenous CMF (cyclophosphamide, methotrexate and fluorouracil) in an open label, randomized phase II trial of first-line chemotherapy for advanced or metastatic disease.[12] Capecitabine was dosed at 2510 mg/m^2 daily in 2 divided doses on days 1–14 of a 21-day cycle. CMF was administered every 3 weeks at standard doses. The primary endpoint was response rate. Capecitabine-treated patients had a higher overall response rate of 30% (95% Confidence Interval CI = 19%–43%) with 3 complete responses (CRs), compared with 16% (95% CI = 5%–33%) in the CMF group with no CRs. The capecitabine-treated group also demonstrated a more rapid time to response, with 13 of the 18 responders demonstrating response by week 6. Median time to disease progression was 4.1 months with capecitabine and 3.0 months

Table 1. Single agent capecitabine as first-line treatment in metastatic breast cancer.

Study	Drugs/schedule	N	ORR %	TTP, months	Median survial, months
O'Shaughnessy et al[12]	Capecitabine, 1255 mg/m^2 BID D1–14	61	30	4.1	19.6
	CMF q 3 weeks	32	16	3.0	17.2
Bajetta et al[14]	Capecitabine, 1250 mg/m^2 BID D1–14	30	37	3.9	10
	Capecitabine, 1000 mg/m^2 BID D1–14	43	35	4.1	16

Abbreviations: ORR, overall response rate; TTP, time to progression; BID, twice daily.

with CMF. Survival was similar in the two treatment groups. The toxicities were comparable in the two groups, although more patients needed dose modifications and treatment discontinuation due to toxicity in the capecitabine arm. Nausea (56%), diarrhea (47%), hand-foot syndrome (43%) and vomiting (31%) were the most common adverse events. The most common grade 3 and 4 events were hand-foot syndrome (15%), diarrhea (8%), stomatitis (8%) and nausea (7%).

Due to the high rates of capecitabine-related toxicities requiring dose reductions and discontinuations, Bajetta et al evaluated two doses of capecitabine in women 65 years or older with advanced breast cancer.[14] Although one prior chemotherapy regimen was allowed, 82% of patients had not received chemotherapy for their metastatic disease. The primary endpoint of the trial was safety. The first 30 women enrolled received the conventional dose of 1250 mg/m^2 twice daily. Thirty per cent of these patients required dose reductions due to toxicities and there were 2 toxic deaths. Subsequently, 43 additional patients were enrolled and received a reduced dose of 1000 mg/m^2 twice daily. Less than 5% of these patients required dose reductions due to toxicities. Importantly, there was no difference in response rates or time to progression between the two groups. In this study, the response rate for chemotherapy-naïve patients was 38%, compared to 28% in those with prior chemotherapy. In clinical practice, 1000 mg/m^2 twice daily is now an acceptable dose.

Patients whose tumors have progressed after anthracyclines and/or taxanes pose a particular challenge, as these agents are considered the most active in breast cancer. Table 2 summarizes five phase II studies of single agent capecitabine activity in this population. The overall response rates ranged from 15%–36%, with median time to progression of 3–5 months. Although cross trial comparisons are difficult due to different patient populations and endpoints, these results compare favorably to other

Table 2. Single agent capecitabine beyond first-line treatment in metastatic breast cancer.

Study	Drugs/schedule	N	ORR %	TTP, months	Median survial, months
Talbot et al[20]	Capecitabine, 1255 mg/m^2 BID D1–14	22	36	3.0	7.6
	Paclitaxel q 3 weeks	19	26	3.1	9.4
Blum et al[11]	Capecitabine, 1255 mg/m^2 BID D1–14	162	20	3.1	12.8
Reichardt et al[22]	Capecitabine, 1250 mg/m^2 BID D1–14	136	15	3.5	10.1
Fumoleau et al[21]	Capecitabine, 1250 mg/m^2 BID D1–14	126	28	4.9	15.2
Wist et al[23]	Capecitabine, 1250 mg/m^2 BID D1–14	48	29	3.6	9.4

Abbreviations: ORR, overall response rate; TTP, time to progression; BID, twice daily.

agents in this setting, including taxanes, with response rates of 20%–30%,[15] vinorelbine with response rates of 10%–20%[16,17] and gemcitabine with response rates of 10%–30%.[18,19]

A randomized phase II study compared capecitabine with paclitaxel in metastatic/advanced breast cancer unresponsive or resistant to anthracyclines.[20] Twenty patients received paclitaxel 175 mg/m^2 in the standard arm and twenty-two patients received capecitabine 1255 mg/m^2 twice daily, on days 1–14. The primary endpoint was overall response rate, which was 26% (95% CI 9%–51%) in the paclitaxel arm with no CRs, compared with 36% (95% CI 17%–59%) in the capecitabine arm with three CRs. The median time to progression (3.1 months with paclitaxel versus 3 months with capecitabine) and overall survival (9.4 months with paclitaxel versus 7.6 months with capecitabine) were similar in both arms. The toxicity profile differed significantly between the two arms. Paclitaxel was associated with more alopecia, peripheral neuropathy, myalgia and neutropenia. In contrast, capecitabine caused more diarrhea, vomiting and hand foot syndrome. Both groups experienced similar improvements in the Karnofsky Performance status, 16% in the paclitaxel arm and 23% in the capecitabine arm.

Blum et al conducted the largest single arm phase II study of capecitabine in taxane-refractory metastatic breast cancer.[11] One hundred sixty-two paclitaxel-refractory patients, with prior anthracycline exposure, received capecitabine 2510 mg/m^2/day for two weeks, followed by one week off. Overall response rate was 20%, with three CRs. Median duration of response was 8.1 months, median survival time was 12.8 months, and the median time to disease progression was 93 days. Similar phase II trials in this population have shown nearly the same time to progression and overall survival as summarized in Table 2.[21–23]

The PELICAN trial is an ongoing randomized Phase III, open-label multinational trial comparing standard doses of capecitabine (1250 mg/m^2 twice daily × 14 days) to pegylated liposomal doxorubicin (50 mg/m^2 q 4 weeks), in first-line metastatic breast cancer. The primary endpoint of time to progression was approximately four months in each arm.[24] The German Breast Group is testing capecitabine as single agent at 1000 mg/m^2 twice daily days 1–14 on a 21 day cycle in the MONICA trial (MONo effICacy of Capecitabine); the results are awaited (www. clinicaltrials.gov). Norton and colleagues have evaluated an alternative dosing schedule of single agent capcitabine, twice daily for 7 days followed by a week off on a 14-day cycle, the so-called 7/7 schedule.[25] In a phase I dose-escalation trial in metastatic breast cancer, the maximum tolerated dose was 2000 mg flat dose twice daily on the 7/7 schedule. A phase II study to evaluate efficacy is ongoing.

Capecitabine chemotherapy combinations

Capecitabine has been studied extensively in combination, especially with taxanes and more recently, ixabepilone. Table 3 summarizes some of this data.

Docetaxel combinations

A large Phase III study by O'Shaughnessy et al compared docetaxel alone to the combination of docetaxel and capecitabine in anthracycline pre-treated metastatic breast cancer.[13] The approved full dose of capecitabine was used. A significantly higher response rate, time to progression and overall survival was seen in the combination arm. The survival benefit with the combination was noted early in the course of treatment, with the curves separating early (Fig. 2). However, the combination was associated with higher rates of grades 3 and 4 stomatitis (17%), diarrhea (14%) and hand-foot syndrome (24%). Dose reduction was required in more than two-thirds of patients in the combination arm, but was effective in reducing the recurrence of grade 3 and 4 adverse events. Quality of life measures by EORTC QLQ-C30 Global Health Score were similar in the two arms. In a retrospective analysis, dose reductions did not impact efficacy. Nonetheless, the toxicities of the combination have limited the use of this regimen in women with metastatic breast cancer.

This trial raises the question of whether the combination regimen is superior to sequential treatment, such as single agent docetaxel followed by capecitabine on progression. In the O'Shaughnessy trial, 35% of patients who progressed after docetaxel alone did not receive any further cytotoxic chemotherapy, partly due to early deaths from progression.[13,26] However, 18% of patients received capecitabine upon progression

Table 3. Selected capecitabine combinations in metastatic breast cancer.

Study	Drugs/schedule	N	ORR %	TTP, months	Median survial, months
O'Shaughnessy et al[13]	Capecitabine, 1250 mg/m^2 BID D1–14 + Docetaxel 75 mg/m^2	255	42 ($P = 0.006$)	6.1 (HR 0.65, $P = 0.0001$)	14.5 (HR 0.78, $P = 0.0126$)
	Docetaxel 100 mg/m^2	256	30	4.2	11.5
Batista et al[30]	Capecitabine, 1000 mg/m^2 BID D1–14 + Paclitaxel 175 mg/m^2	72	52	8.1	16.5
Gradishar et al[31]	Capecitabine, 825 mg/m^2 BID D1–14 + Paclitaxel 175 mg/m^2	47	51	10.6	29.9
Blum et al[32]	Capecitabine, 825 mg/m^2 BID D1–14 + Paclitaxel 80 mg/m^2 D1 and 8	54	59	8.4	21.6
Thomas et al[33]	Capecitabine, 1250 mg/m^2 BID D1–14	377	14	4.2	NR
	Capecitabine, 1000 mg/m^2 BID D1–14 + Ixabepilone 40 mg/m^2	375	35 $P < 0.001$	5.8	NR

Abbreviations: ORR, overall response rate; TTP, time to progression; BID, twice daily; NR, not reported.

and their overall survival was improved to a median of 21 months, compared with other chemotherapy agents used at progression. The most common agent used was vinorelbine in 28% of patients, with a median survival of 12.3 months. The hazard ratio for death was 0.5 in favor of capecitabine over other agents.

To further study the question of combination versus sequential therapy, Beslija et al conducted a trial with 100 patients who had received prior adjuvant anthacyclines, but no prior chemotherapy for metastatic breast cancer.[27] Patients were randomized to capecitabine and docetaxel, at a reduced dose of docetaxel compared to the O'Shaughnessy trial,[13] or to full-dose docetaxel followed by capecitabine on progression. The response rates, time to progression and overall survival were superior in the combination arm, (RR 68 vs. 40%, $P = 0.004$; median TTP 9.3 vs. 7.7 months, $P = 0.001$; median OS 22 vs. 19 months, $P = 0.006$).

The Mexican Oncology Study Group similarly conducted a randomized phase III trial of sequential or combination therapy utilizing docetaxel or paclitaxel in patients with anthracycline-pretreated metastatic breast cancer.[28] In the sequential arm, patients received full dose capecitabine (1250 mg/m^2 twice daily for 14 days), followed by standard doses of docetaxel or paclitaxel upon progression. In contrast, the combination arm

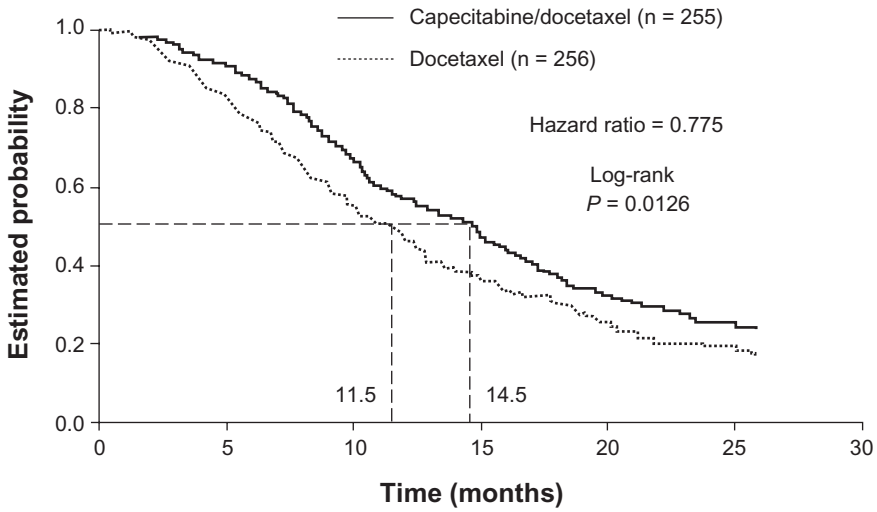

Figure 2. Kaplan-Meier plot of overall survival demonstrating an earlier and statistically significant difference favoring the combination of capecitabine and docetaxel. Reprinted with permission. 2008 American Society of Clinical Oncology. All rights reserved. O'Shaughnessy J, et al. *J Clin Oncol.* 2002;20:2812–23.

utilized lower doses of capecitabine at 825 mg/m^2, and docetaxel at 75 mg/m^2. In a preliminary analysis, the response rates were higher in both combination arms, but the median progression-free and overall survivals were similar among all arms.

Although the combination of capecitabine and docetaxel is associated with improved response rates, the toxicities have prompted others to conduct studies of lower doses of each agent. Michalaki et al reported a phase II study using capecitabine 950 mg/m^2 twice daily on days 1–14 with docetaxel 75 mg/m^2 on day 1.[29] Clinical endpoints were similar to other studies, with a response rate of 42%, a median time to progression of 8 months, and median overall survival of 23 months. The low dose regimen was well tolerated with no febrile neutropenia or significant gastrointestitinal toxicity. Seven percent of patients had grade 3 hand-foot syndrome.

Paclitaxel combinations

Multiple studies have investigated combinations of capecitabine with paclitaxel, as shown in Table 3. Batista et al utilized paclitaxel 175 mg/m^2 every 3 weeks with capecitabine 1000 mg/m^2 twice daily for 14 days in a single arm Phase II trial in first-line treatment.[30] The overall response rate was 52%, with CR of 11%, and stable disease in 29%. Median time to progression was 8.1 months and overall survival was 16.5 months. Grade 3 and 4 adverse events included hand-foot syndrome (11%), alopecia (22%), neutropenia (13%), and neutropenic fever (4%). These results were confirmed by Gradisher et al who utilized a lower dose of capecitabine at 825 mg/m^2 twice daily for 14 days with paclitaxel 175 mg/m^2 every 3 weeks with a similar response rate and progression-free survival.[31] Fewer grade 3 or 4 adverse events were noted including hand-foot syndrome (5%), alopecia (6%) and neutropenia (7%).

Blum et al reported on the efficacy of capecitabine combined with weekly paclitaxel in patients previously treated with a taxane in the metastatic setting.[32] The overall response rate was remarkable at 59%, with a median overall survival of 21.6 months. Grade 3 or 4 hand-foot syndrome was noted in 20%, neutropenia in 13% and fatigue in 7% of patients. Grade 1 or 2 neuropathy was reported in 37% of patients but there was no grade 3 or 4 neuropathy.

Capecitabine is effective in combination with paclitaxel, weekly or q 3 weeks. However, little data exists comparing this strategy to sequential therapy.

Combination with Ixabepilone

Epothilones are a novel class of antineoplastics which stabilize microtubule dynamics leading to apoptotic cell death. Ixabepilone, the first agent in this new class was approved for metastatic breast cancer as a single agent, in disease refractory to anthracyclines, taxanes and capecitabine, and in combination with capecitabine for metastatic breast cancer based on a large phase III trial by Thomas et al.[33] Anthracycline- and taxane-refractory patients were randomized to capecitabine alone or in combination with ixabepilone 40 mg/m^2 every 3 weeks. The primary endpoint was progression-free survival. The overall response rate was significantly higher for the combination, 35 versus 14% ($P < 0.001$) with a progression-free survival improvement from 4.2 to 5.8 months. Compared to capecitabine alone, the combination was associated with more toxicities, including grade 3 or 4 sensory neuropathy (21% vs. 0%), fatigue (9% vs. 3%), and neutropenia (68% vs. 11%). Higher treatment-related mortality was also noted in the combination arm, 3% vs. 1%, primarily due to liver dysfunction. Analysis on overall survival has not been published.

Other combinations

Capecitabine has been evaluated in combination with vinorelbine in several phase I/II studies, with response rates ranging from 26%–61%, and median time to progression of 6 to 10.5 months.[34–36] This combination is limited due to toxicities, especially myelosuppression, nausea, vomiting and asthenia. The Southwest Oncology Group (SWOG) recently completed a phase II study of a simple oral regimen in metastatic breast cancer, capecitabine and oral cyclophosphamide. Both drugs are administered at fixed doses (capecitabine 1500 mg twice daily, days 8–21 and cyclophosphamide 100 mg daily days 1–14). The results will be presented at the 2010 ASCO meeting.

Capecitabine in Her2/neu-positive disease

Table 4 summarizes trials of capecitabine in combination with Her2/neu-directed therapy, including trastuzumab and lapatinib, in Her2/neu-positive metastatic

Table 4. Capecitabine in Her2/neu-positive breast cancer.

Study	Drugs/schedule	N	ORR %	TTP, months	Median survial, months
Schaller et al[37]	Capecitabine, 1250 mg/m^2 BID D1–14 + Trastuzumab weekly	27	45	6.7 (PFS)	28
Bartsch et al[38]	Capecitabine, 1250 mg/m^2 BID D1–14 + Trastuzumab q 3 weeks	40	20	8	24
Geyer et al[3]	Capecitabine, 1250 mg/m^2 BID D1–14	201	13.9	4.3	15.3
	Capecitabine, 1000 mg/m^2 BID D1–14 + lapatinib 1250 mg daily	198	23.7	6.2	15.6

Abbreviations: ORR, overall response rate; TTP, time to progression; PFS, progression free survival; BID, twice daily.

breast cancer. Trastuzumab is an intravenous, partially humanized monoclonal antibody directed at the Her2/neu extracellular protein. In contrast, lapatinib is an oral inhibitor of the epidermal growth factor receptor (EGFR) and Her2/neu intracellular tyrosine kinases. Schaller, et al reported a reponse rate of 45% in a phase II trial of capecitabine and trastuzumab in Her2/neu-positive metastatic breast cancer that had progressed on anthracyclines and/or taxanes.[37] Fifteen percent of patients had a CR and the combination was well tolerated. Bartch et al studied a more heavily pretreated population with anthracycline, taxane and vinorelbine exposure and progression on trastuzumab.[38] Capecitabine and trastuzumab resulted in a remarkable response rate of 20%, a clinical benefit rate of 70%, median time to progression of 8 months, and overall survival of 24 months. The combination was well tolerated. Finally, the combination of capecitabine with lapatinib, compared to capecitabine alone, in patients previously treated with anthracyclines, taxanes and progression on trastuzumab resulted in a longer time to progression, a higher response rate, and a trend toward improvement in overall survival.[3,39] These results led to the FDA-approval of lapatinib in combination with capecitabine, an all oral regimen, in trastuzumab-refractory Her2/neu-positive metastatic breast cancer. Interestingly, fewer patients on the combination arm had CNS disease as the first site of progression, compared to those treated with capecitabine alone. This difference was not statistically significant.

Combinations with other biologics

Capecitabine has also been evaluated in several lines of treatment for metastatic breast cancer in combination with the vascular endothelial growth factor (VEGF) antibody, bevacizumab. A phase III trial of capecitabine alone (1250 mg/m^2 twice daily days 1–14) was compared to the combination of capecitabine and bevacizumab (15 mg/kg) every 3 weeks in a heavily-pretreated population.[40] Although the response rate was higher with the combination arm (19.8% vs. 9.1%, $P = 0.001$), this did not result in an improvement in the primary endpoint of progression-free survival or overall survival. More recently, the RIBBON I and II phase III trials evaluated chemotherapy, including capecitabine, alone or in combination with bevacizumab in less heavily-pretreated populations.[8,41] In RIBBON I, a number of non-paclitaxel chemotherapy regimens was evaluated in the first-line treatment of non-HER2/neu-positive metastatic breast cancer.[8] Capecitabine plus bevacizumab resulted in statistically significant improvement in the primary endpoint of progression-free survival, compared to capecitabine alone (8.6 versus 5.7 mos, respectively). Similarly, RIBBON II evaluated chemotherapy alone and in combination with bevacizumab in the second-line setting in bevacizumab-naïve metastatic breast cancer.[41] Chemotherapy and bevacizumab in this setting resulted in an improvement in progression-free survival compared to chemotherapy alone (7.2 versus 5.1 months, respectively).

With further understanding of the various pathways involved in tumor growth and angiogenesis, newer antineoplastics, including multikinase inhibitors, are being investigated in combination with capecitabine in metastatic breast cancer.

Sorafenib, a potent multikinase inhibitor with anti-angoigenic and anti-proliferation activity, has shown modest activity in advanced breast cancer. In a Phase 2b study, 229 patients with Her2/neu negative

disease and <2 prior chemotherapy treatments were randomized to capecitabine alone (1000 mg/m^2 twice daily days 1–14) or in combination with sorafenib (400 mg twice daily continuously).[42] Preliminary data showed improved progression-free survival, the primary endpoint, favoring the combination (6.4 versus 4.1 months, $P = 0.006$). Further data, including overall survival, is awaited. This combination was associated with significant toxicities, including 90% hand-foot syndrome; half of these were grade 3. Ninety percent of patients required dose reduction.

Everolimus (RAD001), an oral MTOR pathway inhibitor, was studied in a Phase 1 dose escalation trial in combination with capecitabine (825 mg/m^2 twice daily) in metastatic breast cancer.[43] In a preliminary analysis, the combination was well tolerated. The clinical benefit rate of 44% is encouraging in this pilot study (N = 12) of heavily-pretreated patients.

In a SWOG Phase II study, imatinib (400 mg daily) was given in combination with capecitabine (1000 mg/m^2 twice daily days 1–14 of a 21 day cycle) in patients with metastatic breast cancer and ≤2 prior regimens for advanced disease.[44] The combination was well tolerated, but did not result in meaningful improvement in response rate compared to historical rates with capecitabine alone.

Adjuvant Capecitabine

With the encouraging results of capecitabine in the metastatic setting, the ease of oral administration, and the manageable side effect profile, capecitabine was evaluated as adjuvant treatment in early stage breast cancer in elderly women over 65 years.[45] Compared to an anthracycline- or a methotrexate-based regimen, the primary endpoint of relapse-free survival was statistically inferior in the capecitabine arm (Hazarad Ratio 2.09, 95% CI 1.38–3.17, $P < 0.001$). Interstingly, the capecitabine dose of 1000 mg/m^2 twice daily × 14 days could not be dose escalated, as originally planned, due to poor tolerance. Thus, in the adjuvant setting, single agent capecitabine should not be substituted for standard anthracycline- and methotrexate-based regimens.

Management of Toxicities

Patients on capecitabine should be closely monitored for development of the most common side effects, primarily hand-foot syndrome, stomatitis and diarrhea. Most of these can be managed by dose interruptions and reductions, and symptomatic care, but vigilance to toxicities is crucial to maintaining patients on capecitabine. Earlier studies with the higher approved doses (2500 mg/m^2 daily for 14 days) required dose

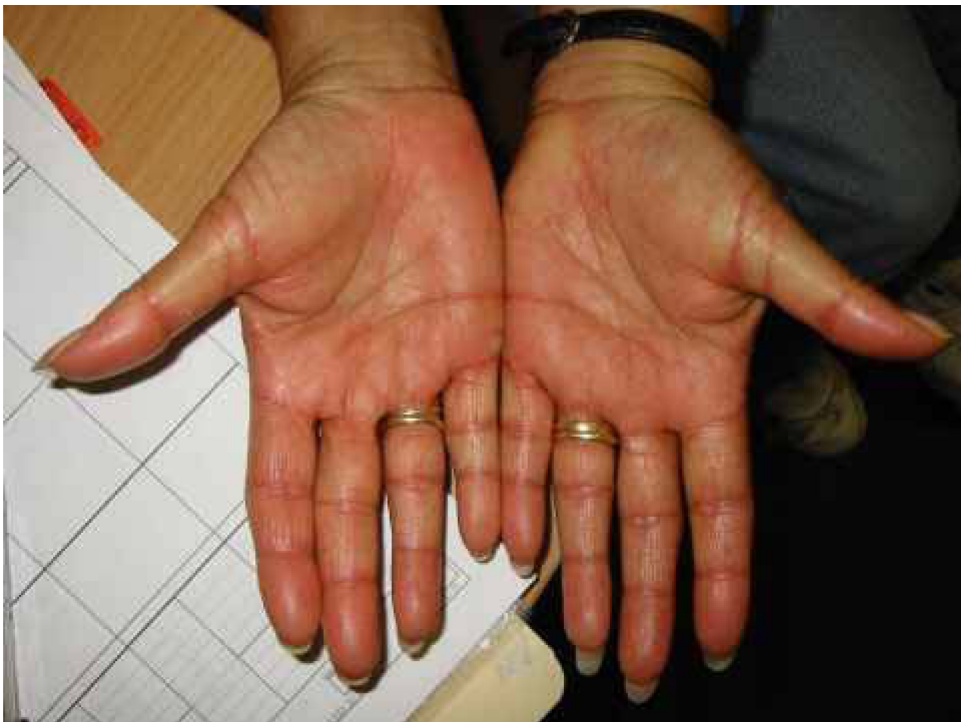

Figure 3. Example of acral erythema due to capecitabine.

reductions in one-third of patients, and discontinuations due to side effects in 16%.[12] A lower starting dose in elderly women has been shown to be efficacious with fewer dose reductions or discontinuations.[14] A reasonable starting dose is 1000 mg/m^2 daily for 14 days.

Hand-foot syndrome (also known as palmar-plantar erythrodysesthesia, acral erythema, toxic erythema of the palms and soles, and Burgdorf's reaction) is the most common adverse event associated with capecitabine. It is depicted in Figure 3. It can range in severity from painless erythema (grade 1) to painful ulceration and blistering (grade 3), as shown in Table 5. Pyridoxine was thought to help prevent the development of hand-foot syndrome, but the results of a randomized trial failed to show any benefit.[46] For grades 2 and 3 hand-foot syndrome, dose interruption is recommended, with dose reduction for grade 3 symptoms, and re-initiating treatment only after the erythema improves to at least grade 1.

If the patient experiences grade 2 or more diarrhea, (an increase of 4–6 stools per day or nocturnal stools), capecitabine should be held until resolution. Anti-diarrheals, such as loperamide, should be initiated with the onset of diarrhea. Patient education and close follow up cannot be underemphasized. Other supportive measures, including anti-emetics and oral care, are successful in treating the mild nausea and stomatitis associated with capecitabine.

Cost Effectiveness

Over the last decade, the approval of oral agents, including capecitabine, imatinib, lapatinib, sunitinib and sorafenib, for a variety of malignancies has increased the spending on non-intravenous anti-cancer therapies.[47] The challenge for many patients is the cost of non-injectable medications. For patients on Medicare, the out-of-pocket costs of oral medications are dependent on their particular pharmacy benefits and drug coverage levels. Many patients' costs will exceed their annual coverage, leaving patients to cover the entire costs of oral medications for the remainder of the year. The same issues are seen with non-Medicare insured patients; the out-of-pocket costs of oral medications are dependent on their co-payments.

Despite the high costs of oral medications, several studies have reported favorable cost comparisons between capecitabine and intravenous chemotherapies in metastatic breast cancer. An early study from the United Kingdom concluded that capecitabine monotherapy and combination therapy were each associated with lower costs compared to vinorelbine and to combination docetaxel and capecitabine, respectively.[48] The authors acknowledge the lack of controlled studies at that time. Camacho and colleagues identified patients with metastatic breast cancer using the cancer registry in North Carolina linked to Medicaid claims and Medicare records.[49] Costs of first-line capecitabine were 32% lower compared to a taxane. Similarly, capecitabine regimens were less costly compared to taxane plus anthracyclines or other taxane regimens in a retrospective analysis of claims data from Thomsom Reuters MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases.[50] These studies cite lower rates of treatment-related complications and side effects, fewer office visits, and less expensive administrative costs associated with capecitabine. While there are limitations in the use of administrative databases, these analyses are consistent with a cost advantage to capecitabine compared to intravenous therapies.

Table 5. Grading of hand-foot syndrome and suggested management.

Grade	Manifestation	Suggested management
1	Numbness, dysesthesia or paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities	Supportive care, close monitoring, moisturizing hand lotions, wearing gloves with household chores
2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living	Dose interruption until resolves to at least grade 1
3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living	Dose interruption until resolves to at least grade 1 + dose reduction for subsequent cycle

Conclusions

Capecitabine is an active oral agent with demonstrated efficacy in metastatic breast cancer, both as a single agent and in combination with a variety of chemotherapeutic and biologic drugs. Its activity is impressive not only in the first-line treatment of advanced disease, but especially in anthracycline- and taxane-refractory breast cancer. Capecitabine should be an option for all patients with metastatic breast cancer, not just those who are elderly or frail.

Capecitabine has a unique side effect profile, with hand-foot syndrome, diarrhea, stomatitis and mild nausea being the most common adverse events. Severe side effects can be prevented or greatly reduced by using a more practical single agent dose of 1000 mg/m^2 twice daily for 14 days. Dose interruptions, supportive care, and patient education regarding expected side effects result in manageable toxicities, even in combination regimens. In addition, capecitabine is associated with little alopecia or marrow toxicity. Dose adjustments for hepatic dysfunction are not required as the drug is metabolized renally.

The oral administration of capecitabine is particularly attractive for patients, as it allows those with metastatic disease less time in infusion centers and in traveling for their treatment. This gain in time can only improve the quality of life for patients with advanced cancer. Cost comparisons thus far have concluded that capecitabine regimens are less costly compared to intravenous therapies.

In summary, capecitabine is an active agent in metastatic breast cancer. Over the last decade, our experience with the drug has led to effective therapeutic strategies and manageable toxicities.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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